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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,449	ZI ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *2-7 and 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21 and 22* is/are rejected.

7)☒ Claim(s) *8-12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *July 17, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application claims benefit of provisional application 60/459495, filed April 1, 2003. Claims 1, 8-12, and 20-21 are pending in this application and examined on the merits herein.

Election/Restrictions

Applicant's provisional election with traverse of group I, drawn to a method of treating bladder or urinary tract cancer by administering a compound of formula **I**, filed July 21, 2006, is acknowledged. Applicant's arguments of record with respect to the aforementioned traversal are acknowledged but not found to be convincing to remove the requirement for restriction. Applicant argues that certain prenylated embodiments of formula **1** are capable of electrocyclic cyclization to form the compounds of formula **3A-C**. However, the references submitted by Applicant argue in favor of these compounds being chemically distinct. For example, Miranda et al. (Reference included with PTO-1449) discloses on p. 24 a number of prenylchalcones (for example, XN, XG, and TX) which according to Applicant, will undergo this cyclization. These compounds are disclosed in the non-cyclized form, indicating that this form is sufficiently stable that cyclization is not spontaneous under ordinary conditions. Instant claims 11 and 12 are also drawn to methods of administering prenylchalcones to a patient, further indicating that these molecules are stable at room temperature. The mere fact that one compound could, under the right conditions, be chemically transformed into another does not make the two compounds identical. Furthermore, if it were the case that

prenylated chalcones were unstable at room temperature and spontaneously underwent cyclization to form the compounds of formula **3A-C**, these compounds would therefore not be suitable active ingredients for the method of group I, since by the time they were administered to the patient they would have decayed into a chemical structure not included in the limitations of group I, and a method comprising administering them would be a method comprising administering a compound of formula **3A-C,** not formula **1**. The history of the administered compound, namely that it had at one point been produced by the cyclization of a prenylchalcone, would be irrelevant to its present use, because its therapeutic effect on the patient would be no different than if it had been synthesized by some other route. Applicant is further reminded that it is proper to require restriction between an intermediate and a final product if the intermediate is useful to make products other than the final product, and the two species are patentably distinct, criteria which apply to the instant claims. See MPEP § 806.05(j). In the instant case, a prenylchalcone could be used as an intermediate in the synthesis of other final products, for example by alkylating or acylating the free hydroxyl group or by modifying the prenyl group by, for example, epoxide formation or dihydroxylation. Therefore the requirement for restriction is maintained and made **FINAL**.

Claims 2-7 and 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on July 21, 2006.

Claims 1, 8-12, and 20-21 are pending in this application and examined on the merits herein.

Claim Objections

Claim 1 are objected to because of the following informalities: The term ")-Glucoronate". A closed parenthesis is not a recognized chemical symbol. It is likely that the closed parenthesis should be an O, making the term, "O-Glucoronate" Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation, "R_1, R_3, R_5, R_6, and R_7 are selected from H, OH, O-**Alkyl**, O-**Alkenyl**, O-**Acyl**; O-Glucosyl, O-Sulphate, [O-Glucoronate] and O-**amino acid**, halogen, amino, **substituted** amino and **oxygen atom**."

The terms "Alkyl," "Alkenyl," "Acyl," and "Substituted Amino," all fail to clearly and distinctly define the claimed subject matter. These terms potentially encompass an

enormous and open-ended diversity of chemical structures. In particular, no limit is given to the size, substituents, or branched character of the alkyl, alkenyl or acyl group, or of the substituent attached to the amine. Thus the reader is unable to definitively determine which structures are or are not encompassed by these limitations.

Furthermore, it is not clear whether in the context of the claim, the term "amino acid" refers to only the twenty naturally occurring amino acids or whether it also encompasses additional entities, including but not limited to:

(A) D-amino acids

(B) α-amino acids with non-standard side chains

(C) β-, γ-, δ-, or other non-α-amino acids

Potentially any compound containing both an $-NH_2$ and a -COOH functional group may or may not be included within this limitation.

Still further, the term, "oxygen atom" does not denote a specific functional group, as the substitution of an oxygen atom, not attached to any further group, at positions R_1, R_3, R_5, R_6, or R_7, does not lead to a complete chemical structure but rather to a free radical. It is unclear whether the term, "oxygen atom" refers to an oxygen atom linked to another atom or functional group, (e.g. an ether) an oxygen free radical, or a ketone.

For these reasons the limitations of claim 1, and its dependent claims s20 and 21, are indefinite.

Claims 1, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating bladder or urinary tract

cancer by administering a compound disclosed in the prior art or in Applicant's specification to possess cytotoxic activity, does not reasonably provide enablement for such a method comprising administering any chalcone compound described in instant claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating bladder cancer by administering a therapeutic agent.

The state of the prior art: Chalcones have many biological effects *in* vivo. Certain chalcones are known in the prior art to possess anti-tumor activity. The source of the anti-tumor effect has not been fully elucidated, and different chalcone derivatives appear to act by different mechanisms. Gerhauser et al. (Reference included with PTO-1449) discloses that xanthohumol, a prenylated chalcone, affects the rate of carcinogen metabolism, acts as an antioxidant, and inhibits COX-1 and DNA polymerase α, (pp.

963-965) properties associated with anti-tumor efficacy. Other chalcone derivatives have been found to disrupt the P53/MDM2 complex (Khan et al., WO03/10638, reference included with PTO-892) or inhibit aromatase. (Kinghorn et al, US Patent 6737439, cited in PTO-1449) The majority of chalcone derivatives disclosed in the prior art bear hydroxyl, methoxy, and prenyl substituents, and chalcone derivatives bearing other substituents, particularly charged substituents or large hydrophobic and/or sterically hindering groups, have not been well characterized.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: According to Miranda et al. (reference included with PTO-1449) "The biological effects of chalcones depend on their molecular structure," and, "substitutions on the chalcone structure have a profound influence on the anticarcinogenic effects of chalcone compounds." (p. 272, left column, second paragraph) Thus the relative anti-tumor efficacy of differently substituted chalcones is unpredictable.

The Breadth of the claims: The structure disclosed in instant claim 1 is very broad, covering an enormous array of chalcone derivatives substituted with a number of arbitrarily large and complex substituents. In particular, no limits are placed on the size, shape, complexity, or further substitution of the alkyls, acyls, alkenyls, amino acids, and substituted aminos included in these structures.

The amount of direction or guidance presented: A method for testing candidate compounds *in vivo* is disclosed along with examples of certain compounds having activity in this assay. These compounds include 2,4,3'-trihydroxy-6-methoxychalcone

and 4-hydroxy, 4',2,6-trimethoxychalcone. No other chalcone derivatives were assayed.

The presence or absence of working examples: No working examples are disclosed of any *in vivo* therapeutic methods.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the biological activities of chalcone derivatives. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of chalcone derivatives beyond the meager number disclosed in the specification would be required to test potential compounds *in vitro* to determine whether a particular compound inhibits the growth of cancer cells. For most compounds, it is unknown whether they are or are not useful in this manner. Gathering this data for every possible chalcone derivative, no matter how large or complex the substituents, would involve *in vitro* screening of an enormous diversity of chemical compounds, which would need to be synthesized. It should be noted that in some cases, the substituents may be larger, more complex, and more difficult to synthesize than the core structure. Synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential chalcone derivatives, these experiments would involve the synthesis and testing of a wide diversity of compounds. Furthermore, many of these compounds are

expected to be useless as cytotoxic agents or inhibitors of tumor cell growth, due to their diversity and the unpredictability of the art. Developing a therapeutic method involving a non-functional compound presents an insurmountable obstacle to one skilled in the art, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of chalcone derivatives claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art, the breadth of the claims, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all possible chalcone derivatives.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen (US patent application 10/072823, reference cited in PTO-892) Chen discloses a method of treating cancers, including specifically prostate, breast, colon, lung, and **Bladder** cancers. (paragraph 0029, paragraph 0046) The disclosed compounds may comprise bavachalcone, a compound which falls within the limits of instant claim 1. (paragraph 0039, paragraph 0046) Administration of the composition may be oral. (paragraph 0048) Thus the disclosure of Chen anticipates instant claims 1 and 20.

Claims 1 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Sunkara et al. (Reference cited in PTO-1449) Sunkara et al. discloses a method of using amino-chalcone derivatives to control the growth of tumor tissue. (column 2, lines 15-33) These amino-chalcone derivatives fall within the limitations of the formula of instant claim 1 in which R_7 is substituted amino. Sunkara et al. discloses that the tumor tissue affected can include urologic tumors such as bladder tumors. (column 3, lines 14-15) The therapeutic agent may be administered orally as disclosed in instant claim 21. (column 8, lines 3-31) Thus the disclosure of Sunkara et al. anticipates instant claims 1 and 20.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (US patent application 10/072823, reference cited in PTO-892) in view of Au et al. (US patent 6286513, cited in PTO-892) Chen discloses a method of treating cancers, including specifically prostate, breast, colon, lung, and **Bladder** cancers. (paragraph 0029, paragraph 0046) The disclosed compounds may comprise bavachalcone, a compound which falls within the limits of instant claim 1. (paragraph 0039, paragraph 0046) Administration of the composition may be oral. (paragraph 0048) Chen does not disclose intravesical administration of a chalcone derivative.

Au et al. discloses a method of delivering an anti-tumor compound directly to the bladder by intravesical instillation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy of Chen by the method of Au et al. One of ordinary skill in the at would have been motivated to practice the invention in this manner because the method of Au et al. is directed towards administering a compound to the bladder for the treatment of bladder cancer, and because, in the treatment of a solid tumor, local administration (i.e. specifically to he bladder) is preferred over systemic administration. One of ordinary skill in the art would reasonably have expected success because intravesical instillation is a recognized and routine method of administering therapeutic compounds for local administration to the bladder.

Thus the invention taken as a whole is *prima facie* obvious.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sunkara et al. (Reference cited in PTO-1449) in view of Au et al. (US patent 6286513, cited in PTO-892) Sunkara et al. discloses a method of using amino-chalcone derivatives to control the growth of tumor tissue. (column 2, lines 15-33) These amino-chalcone derivatives fall within the limitations of the formula of instant claim 1 in which R_7 is substituted amino. Sunkara et al. discloses that the tumor tissue affected can include urologic tumors such as bladder tumors. (column 3, lines 14-15) The therapeutic agent may be administered orally as disclosed in instant claim 21. (column 8, lines 3-31) Thus the disclosure of Sunkara et al. anticipates instant claims 1 and 20.

Au et al. discloses a method of delivering an anti-tumor compound directly to the bladder by intravesical instillation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy of Sunkara et al. by the method of Au et al. One of ordinary skill in the at would have been motivated to practice the invention in this manner because the method of Au et al. is directed towards administering a compound to the bladder for the treatment of bladder cancer, and because, in the treatment of a solid tumor, local administration (i.e. specifically to he bladder) is preferred over systemic administration because of the severe toxicity of most anticancer agents. One of ordinary skill in the art would reasonably have expected success because intravesical instillation is a recognized and routine method of administering therapeutic compounds for local administration to the bladder.

Thus the invention taken as a whole is *prima facie* obvious.

Claim Objections

Claims 8-12 are objected to as being dependent upon a rejected base claim, but would be in condition for allowance if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Instant claims 8-12 are drawn to subject matter which is adequately described and enabled by Applicant's specification, as compounds possessing these or similar structures have been shown to possess anti-tumor activity. The claimed methods of using these compounds for the treatment of bladder cancer are novel and non-obvious over the prior art because the compounds have not been previously disclosed to possess anti-tumor activity or to be useful for the treatment of bladder cancer, over and above their well-known antioxidant and cancer chemopreventative activities. Although these compounds are natural products present in, for example, *Humulus lupulus, Vitex leptobotrys, and Piper methysticum,* these plant species have not been known in the prior art to be useful as therapeutics for treating bladder cancer, as opposed to merely lowering the future risk of cancer in a healthy subject. Therefore the subject matter described in these claims is novel and non-obvious over the prior art.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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